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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/088,814	09/04/2002	Andrew Austen Mortlock	Z70599-1P US	2356

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EXAMINER	
TRUONG, TAMTHOM NGO	
ART UNIT	PAPER NUMBER
1624	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/088,814	MORTLOCK ET AL.	
	Examiner	Art Unit	
	Tamthom N. Truong	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20,27,30,34-39 and 41-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20, 27, 30, 34-39 and 41-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

NON-FINAL ACTION

Applicants' amendment of 3-13-07 has been fully considered. The cancellation of "*ester or amide thereof*" has overcome the previous rejection of 112/2nd paragraph, item (a), and thus withdrawn. However, the amended claim 27 has not overcome the previous rejection of 112/2nd paragraph, item (b), and thus maintained. Also, applicants' argument has not overcome the previous 103 rejection, and so maintained.

Upon review of the claimed subject matter having many variables represent groups that are substituted with an aryl group which in turn could be further substituted several times more, a rejection of "Scope of Enablement" is presented below.

Claims 20, 27, 30, 34-39 and 41-44 are pending.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. **Scope of Enablement:** Claims 20, 27, 30, 34-39 and 41-44 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the making and using of compounds of formula (IID) wherein R^{64} is an unsubstituted *phenyl*, or said rings *substituted with simple groups such as: halogen, alkoxy, alkyl, nitro, CF_3*, does not reasonably provide enablement for compounds of formula (IID) wherein R^{64} is a phenyl group that is

extensively substituted, and further substituted, nor does it enable for compounds of formula (IID) wherein R^{64} is an optionally substituted heterocyclyl . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The following factors have been considered in the determination of an enabling disclosure:

(1) The breadth of the claims;

(2) The amount of direction or guidance presented;

(3) The state of the prior art;

(4) The relative skill of those in the art;

(5) The predictability or unpredictability of the art;

(6) The quantity of experimentation necessary;

[See ***Ex parte Forman***, 230 USPQ 546 (Bd. Pat. App. & Int., 1986); also ***In re Wands***, 858 F. 2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)].

The breadth of the claims: Claims 20 and dependents thereon recite formula (IID) wherein R^{64} is a phenyl group substituted with groups that can be further substituted with another aryl group which in turn can be substituted with yet another aryl group, and so on. Because of the extensive substitution on variable R^{64}, the scope of formula (IID) is unduly broad, and beyond a simple substituted quinazoline compound.

The amount of direction or guidance presented: The compounds of formula IID are believed to be in Tables 2 and 3 in which the phenyl group (of R^{64}) is not substituted. The other

quinazoline compounds have the terminal phenyl group substituted with simple moieties (e.g., halogen, alkoxy, nitro, cycloalkyl, etc.) which are not further substituted. Even if all compounds have been tested for biological activity, they are not a fair representation of the claimed formula IID wherein R^{64} is a phenyl that can be extensively substituted, or an optionally substituted heterocyclyl group.

The state of the prior art: As evident by **Brown et. al.** (WO'118), the quinazoline compounds with activity to treat colon or breast cancer are not extensively substituted. Thus, the state of the prior art does not support the broad scope of the instant formula IID.

The relative skill of those in the art: Even with the advanced training, the skilled clinician would have to carry out extensive research to select an effective compound from the large Markush group of formula IID. Not only one has to determine an IC_{50} value, but also *in-vivo* activity to establish an LD_{50}, therapeutic index and pharmacokinetic profile for each compound. Given a large Markush group of the claimed formula IID, such a task would require a tremendous amount of effort, time and resource.

The predictability or unpredictability of the art & The quantity of experimentation necessary: The pharmaceutical art has been known for its unpredictability due to various conflicting path ways, or biological factors that are sometimes genetically unique to individuals. In the instant case, the bioassay data shown for compounds made might not reflect the same activity for those of formula IID with substituents on top of substituents.

Describing the invention as broadly as it is claimed does not necessarily enable one how to make and use the invention. Note the following quote taken from **In re Cauvallito** 127 USPQ 202 (regarding literal support at page 205, left column):

"The mere statement of an inventive concept; however, is not a sufficient basis for claiming it. Sufficient information must be given to enable those skilled in the art to practice the invention."

With regard to structure-sensitivity note the following quote at page 206, left column:

"On the other hand, wide variation in such potency would suggest that it was due in part to the added substituents and might be eliminated or even reversed by many of the possible substituents which had not been tried."

Thus, as long ago as the Cauvallito decision, the emphasis on the need for working examples **representative** of the claims's scope was a requirement for compliance with 35 USC 112, first paragraph in unpredictable arts and the requirement is still present in MPEP 2164.02. Unpredictability entails structural sensitivity – a well known fact in drug design. Given the recognized factors that can affect receptor binding, namely size (surface area), polarity and electronic effects, the skilled artisan would **not** have sufficient information to predict how big a quinazoline derivative from among the many covered by the instant scope would be suitable bioisosteric replacements for the small number of compounds made and presumably tested.

Note that in University of Rochester v. G.D. Searle & Co., 68 USPQ 2d. 1424 at 1438, the screening for over 600 compounds was deemed to be undue. Applicant's scope far exceeds this number.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 20, 27, 30, 34-39 and 41-44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

a. Claim 20 recites several moieties having variable "ar" (e.g., ar$C_{1\text{-}10}$alkyl) which has no definition. It is unclear what the scope of "ar" is. Applicant is suggested to define or clarify said variable.

b. Claim 27 has been amended to recite the last step as "*converting a group R^1, R^2, R^3 or R^4 respectively to a different such group.*" It is still unclear as to which group gets converted to which and by what means.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 20, 27, 30, 34-39 and 41-44 remain rejected under 35 U.S.C. 103(a) as being unpatentable over **Brown et. al.** (WO'118 – previously cited).

The rejection is maintained for the reason stated in the previous action and for the one below:

a. It is noted that $-OCH_3$ has been excluded for $R^{3'}$. However, page 27 starting from line 4, Brown et. al. lists several substituents for R^1 at the 6- and 7-position which includes *ethoxy*, *2-methoxyethoxy*, etc. which reads on the many groups represented by the instant X^1-$R^{15'}$. Thus, any of the substituents at the 6-position (as listed on page 28) can also be at the 7-position as well. Therefore, the proviso for $R^{3'}$ is insufficient to overcome the equivalency teaching.

b. Although formula IID has R^7 and R^8 at adjacent ring positions, they both can be hydrogen which means the aniline does not have to have additional substituents. Thus, their presence does not sufficiently distinguish the instant formula IID from the generic teaching of Brown et. al.

Therefore, it is maintained that the teaching of Brown et. al. still establishes a *prima facie* case of obviousness, not withstanding applicants' traverse.

The changes needed to arrive at applicants' invention are within the preferred embodiments listed on pages 24-25, and 27. It is well settled that a reference is not just limited to its preferred embodiments or working examples but for all that it fairly teaches. See **In re Lamberti** 192 USPQ 278; **In re Mills** 176 USPQ 196; **In re Burckel** 201 USPQ 67 regarding

the latter point. Given the similar activities and uses, and the suggestion to replace exemplified moieties (in species pointed out) with that claimed herein, the rejection is believed proper, and thus maintained.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tamthom N. Truong whose telephone number is 571-272-0676. The examiner can normally be reached on M, T and Th (9:00-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Tamthom N. Truong
Examiner
Art Unit 1624

5-31-07

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